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(51) International Patent Classification ⁶ : C12N 15/62, C07K 19/00, 14/47, C12N 9/12 // C07D 498/18	A3	(11) International Publication Number: WO 99/36553 (43) International Publication Date: 22 July 1999 (22.07.99)
(21) International Application Number: PCT/US99/00178 (22) International Filing Date: 15 January 1999 (15.01.99) (30) Priority Data: 60/071,591 15 January 1998 (15.01.98) US 60/072,016 21 January 1998 (21.01.98) US 60/072,219 22 January 1998 (22.01.98) US 09/012,097 22 January 1998 (22.01.98) US (71) Applicant (for all designated States except US): ARIAD GENE THERAPEUTICS, INC. [US/US]; 26 Landsdowne Street, Cambridge, MA 02139 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): CLACKSON, Timothy, P. [GB/US]; 47-12 Cogswell Avenue, Cambridge, MA 02140 (US). GILMAN, Michael, Z. [CA/US]; 550 Chestnut Street, Newton, MA 02168 (US). HOLT, Dennis, A. [US/US]; 516 Tumblin Hawk, Acton, MA 01718 (US). KEENAN, Terence, P. [US/US]; Apartment 1L, 62 Spring Street, Cambridge, MA 02141 (US). ROZAMUS, Leonard [US/US]; 39 Mitchell Grant Way, Bedford, MA 01730 (US). YANG, Wu [CN/US]; 34, Hammond Pond Parkway #3, Chestnut Hill, MA 02167 (US).	(74) Agent: BERSTEIN, David, L.; Ariad Gene Therapeutics, Inc., 26 Landsdowne Street, Cambridge, MA 02139 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 21 October 1999 (21.10.99)	
(54) Title: REGULATION OF BIOLOGICAL EVENTS USING MULTIMERIC CHIMERIC PROTEINS (57) Abstract <p>Materials and methods are disclosed for regulation of biological events such as target gene transcription and growth, proliferation or differentiation of engineered cells.</p>		

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INTERNATIONAL SEARCH REPORT

Int. Appl. No.

PCT/US 99/00178

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/62 C07K19/00 C07K14/47 C12N9/12 //C07D498/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 96 41865 A (ARIAD GENE THERAPEUTICS) 27 December 1996 (1996-12-27) cited in the application page 2, line 12 - page 6, line 7; figure 1 page 10, line 4 - page 16, line 2 page 16, line 34 - page 17, line 11 page 18, line 32 - page 19, line 2 page 19, line 35 - page 32, line 2 page 41, line 1 - page 49, line 5; examples</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1-32



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 August 1999

Date of mailing of the international search report

2. 09. 99

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/00178

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	VICTOR M. RIVERA ET AL.: "A humanized system for phamacologic control of gene expression" NATURE MEDICINE, vol. 2, no. 9, September 1996 (1996-09), pages 1028-1032, XP002018162 cited in the application page 1030, left-hand column, last paragraph - right-hand column, paragraph 1 ---	1-32
A	JUAN I LUENGO ET AL.: "Structure-activity studies of rapamycin analogs: evidence that the C-7 methoxy group is part of the effector domain and positioned at the FKBP12-FRAP interface" CURRENT BIOLOGY, vol. 2, 1995, pages 471-481, XP002045681 abstract page 473, left-hand column, paragraph 1 - page 478, left-hand column, paragraph 1 ---	1,2
A	US 5 527 907 A (YAT S. OR ET AL.) 18 June 1996 (1996-06-18) cited in the application the whole document -----	1,2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/00178

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 28-32 and claims 1-27 as far as comprising an in vivo method, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. ☒ Claims Nos.: 1,2
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

See FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 2

The substituent in position C22 in formula I in claim 1 has not been defined. Claim 1 has therefore been searched considering formula I substituted in position C22 by the substituent given in the description page 82, formula 4.

Present claim 2 relates to an extremely large number of possible compounds. In fact, the claim contains so many options that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Substituents R12, R4', R5', and R3 are not defined; Substituent RC13 is undetermined when RC28 is a halo substituent; the use of the expression and/or implies that all substituents except moiety a may be undefined. Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely the method of claim 2, as disclosed in examples 12, and 13 with compounds 79, 108, 96, 42, 53, and 69.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 and partially claims 13, 14, 18, 20, 24, 25, and 27-32

Method for multimerizing chimeric proteins in cells by providing cells containing nucleic acid encoding two chimeric proteins comprising respectively a FKBP and FRB domain and at least a heterologous domain and contacting the cells with a rapalog of formula I

2. Claims: 2-12, 15-17, 19, 21-23 and partially claims 13, 14, 18, 20, 24, 25, and 27-32

Method for multimerizing chimeric proteins in cells by providing cells containing nucleic acid encoding two chimeric proteins comprising respectively a FKBP and FRB domain and at least a heterologous domain and contacting the cells with a rapalog of the formula disclosed in claim 2.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/00178

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9641865 A	27-12-1996	AU 6270696 A CA 2219080 A EP 0833894 A	09-01-1997 27-12-1996 08-04-1998
US 5527907 A	18-06-1996	CA 2175215 A EP 0729471 A JP 9505299 T WO 9514023 A US 5583139 A US 5672605 A	26-05-1995 04-09-1996 27-05-1997 26-05-1995 10-12-1996 30-09-1997